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EXAMINER	
FORD, ALLISON M	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 11/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/812,318	DE BRUIJN ET AL.	
	Examiner	Art Unit	
	Allison M. Ford	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *2,7,15 and 16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-6,8-14 and 17-22* is/are rejected.

7)☒ Claim(s) *3* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I (claims 1-14 and 17-19) in the reply filed on 19 September 2005 is acknowledged. Applicants have added new claims 20-22, which are made part of Group I. The traversal is on the ground(s) that the subject matter of Groups I and II is interrelated to the extent that a search and examination of both groups would not be overburdensome. This is not found persuasive because burden consists not only of specific searching of classes and subclasses, but also of searching multiple databases for foreign references and literature searches. Burden also resides in the examination of independent claim sets for clarity, enablement and double patenting issues. Therefore searching the instant two patentably distinct inventions would, in fact, impose a serious burden on the examiner. The requirement is still deemed proper and is therefore made FINAL.

Regarding the election of species requirement, applicants have elected (j) combination of hydroxyapatite and β-calcium phosphate as the species of calcium salt; and (q) combinations of alginates (including sodium alginate), dextrans (including dextran), cellulose and cellulose derivatives (including carboxymethylcellulose), plasma, biogenic binders (including fibrin glue), and hyaluronic acid, as the species of binder. The examiner wishes to thank applicant for pointing out the error which named two subgroups as species "q" in the second group; and appreciates their cooperation in correctly interpreting the election requirement in light of this error. Regarding the traversal of the election of species requirement, it is noted that, as is proper in election of species practice, should a generic claim be found allowable the search will be extended to include additional species, see MPEP § 809.02.

Status of Application

The preliminary amendments made to the claims in order to correct formal matters have been entered. Claims 1-22 remain pending in the current application, with claims 2, 7, 15 and 16 being

withdrawn from consideration as being directed to non-elected inventions/species. Claims 1, 3-6, 8-24 and 17-22 have been examined on the merits.

Claim Objections

Due to the election of species, claim 3 is dependent on a withdrawn base claim (claim 2); as such claim 3 is objected to. For purposes of examination, claim 3 has been interpreted as being dependent on base claim 1.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-6, 8-14, and 18-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabled for use of osteogenic cells and osteoprogenitor cells in the bone filler composition, does not reasonably provide enablement for any type of stem cells in the bone filler composition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Applicant's claims are directed to an injectable bone filler composition comprising calcium salt particles, an organic binder, a pharmaceutically acceptable buffer, and cells selected from the group consisting of stem cells, osteogenic cells, and osteoprogenitor cells. Applicant's claims are also directed to methods of preparing the above bone filler composition and methods of using the bone filler composition for treatment of osseous defects.

The bone filler composition of the present invention must be suitable for injection into a subject. Regarding the types of cells suitable for injection it is well accepted in the art that progenitor cells,

including osteoprogenitor cells, and other osteogenic cells, are suitable for injection to produce new bone tissue; however, the category of stem cells encompasses pluripotent stem cells, such as embryonic stem cells, which are not approved for direct injection in vivo in humans or animals. While the potential of embryonic stem cells for regeneration of organs and tissue in vitro is being explored and shows great promise, directed differentiation of pluripotent stem cells, such as embryonic stem cells, in vivo remains very unpredictable. Direct injection of undifferentiated pluripotent embryonic stem cells in vivo can result in uncontrolled proliferation, resulting in formation of tetratomas, and/or can result in uncontrolled differentiation, producing many different and undesired tissue types at the site of injection (See Morely, 2002). Therefore the general state of art teaches that direct injection of embryonic stem cells in vivo is not safe for humans or animals. At the time the invention was made it was not routine to control the proliferation and differentiation of embryonic stem cells, or even the somatic cells derived from ES cells, in vivo. At the time the invention was made the use of embryonic stem cells in vitro was not considered routine and the use of ES cells in vivo was extremely unpredictable. The present application provides no working examples using embryonic stem cells or pluripotent stem cells in the present invention, nor do they provide any guidance or direction on how one of ordinary skill in the art could control the differentiation and proliferation of stem cells injected in vivo; therefore a large amount of undue experimentation would be required to determine the parameters and controls necessary to direct and confine the differentiation of the stem cells to bone cell lineages. Therefore, due to the sum of all the aforementioned factors, one of ordinary skill in the art, at the time the invention was made, would not expect success creating or using an injectable bone filler composition comprising stem cells.

Claims 12 and 14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the

specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's claims are directed to an injectable bone filler comprising calcium salt particles, an organic binder, cells, and a pharmaceutically acceptable buffer. Claim 12 further requires the bone filler to comprise an angiogenic factor. Claim 14 further requires the bone filler to comprise an osteoinductive factor.

Applicant fails to provide sufficient written description of angiogenic factors or osteoinductive factors, much less sufficient description of a representative number of species of each which is required to claim the entire genuses of angiogenic factor and/or osteoinductive factors. Additionally, there is no disclosure of relevant, identifying characteristics, such as structure or other physical or chemical properties, or functional characteristics of either factors sufficient to show the applicant was in possession of the claimed genus. *See Eli Lilly,* 119F. 3d. at 1568, 43 USPQ2d at 1406. See MPEP § 2163. At page 7 of the specification applicant teaches inclusion of osteoinductive factors, such as BMP (Pg. 7, ln 14-15); furthermore applicant describes FGF, VEGF, and PDGF as suitable osteoinductive factors (Pg. 76, ln 20-21). While applicant teaches angiogenic factors can be included, they provide no specific examples of angiogenic factors; however, it appears FGF, VEGF, and PDGF were intended to be examples of angiogenic factors instead of osteoinductive factors.

Despite the listing of these four examples of common growth factors, applicant has not satisfied the written description requirement because they have not shown relevant, identifying characteristics of any osteoinductive or angiogenic factors that would have particular effects on bone cell growth and mature bone formation in vivo. Description of common growth factors does not provide sufficient description or guidance to show that applicant was in possession of factors specifically intended as osteoinductive factors versus angiogenic factors. One of ordinary skill in the art would not be able to clearly decipher which factors would be considered angiogenic factors and which would be considered

osteoinductive factors for use in the presently claimed composition, based on the generic description provided by applicant. Therefore it does not appears applicants were in possession of all osteoinductive and all angiogenic factors, which are claimed in the current invention, at the time of filing.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10, 17-18 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant's claim 1 is directed to an injectable bone filler comprising calcium salt particles, an organic binder having an affinity for calcium salt, cells selected from the group consisting of stem cells, osteogenic cells, and osteoprogenitor cells, and a pharmaceutically acceptable buffer. Claim 10 requires the bone filler to have a solids content of 30-70% w/w, based on the weight of the bone filler. Claim 22 requires the bone filler to have a solids content of 40-60% w/w.

In claims 10 and 22 it is not clear what applicant is defining as the 'solids' which make up the solids content. While it would appear the calcium salts are considered solids, upon dissolution in liquid buffer, these salts will dissociate and would be considered aqueous. It is further unclear if the organic binders and/or the cells are to be considered solid components of the bone filler composition.

Applicant's claim 17 is directed to a method of making the bone filler of claim 1, comprising mixing the binder and the buffer to prepare a gel, adding the calcium salt particles to the gel, and homogenizing to obtain the bone filler. Claim 18 requires cells, selected from the group consisting of stem cells, osteogenic cells, and osteoprogenitor cells to be seeded on the calcium salt particles before the

salt particles are added to the gel, or for the cells to be introduced after combining the calcium salt particles and the gel.

In claim 17, it is not clear what is homogenized, it appears the mixture of the binder, the buffer, and the calcium salt particles are homogenized to obtain the bone filler of claim 1. Still further, the composition of claim 1 comprises cells, the method of claim 17 does not involve addition of cells; therefore it is not clear how the method of claim 17 makes the composition of claim 1. (Though it is recognized that claim 18 requires addition of cells, each claim must be able to stand on its own.)

In claim 18 it is not clear what "they" is referencing in the second line of the claim, the calcium salt particles, or the cells. Furthermore, regarding the phrase "wherein cells are introduced after combining calcium salt particles and the gel," it is not clear what the cells are introduced *to*.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Applicant's claim 1 is directed to an injectable bone filler comprising calcium salt particles, an organic binder having an affinity for calcium salt, cells selected from the group consisting of stem cells, osteogenic cells, and osteoprogenitor cells, and a pharmaceutically acceptable buffer. Claim 3 requires the calcium salt to be a mixture of hydroxyapatite and β-calcium phosphate. Claim 3 requires the particles of claim 2 to have a diameter in the range of 100 to 600 um. Claims 5 and 6 require the binder

of the bone filler composition to be a combination of at least two of the following: sodium alginate, alginates, dextrans, dextran, cellulose, cellulose derivatives, carboxymethyl cellulose, plasma, biogenic binders, fibrin glue, and hyaluronic acid. Claim 8 requires the binder to be present in an amount from 0.5 to 10% w/w, based on the weight of the bone filler. Claim 9 requires the buffer to be phosphate buffered saline (PBS). Claim 10 requires the bone filler to have a solids content of 30-70% w/w, based on the weight of the bone filler. Claim 11 requires the bone filler to have a viscosity between 30,000 and 100,000 centipoises. Claim 12 requires the bone filler to further comprise an angiogenic factor. Claim 13 requires the cells to be seeded on the calcium salt particles. Claim 14 requires the bone filler to further comprise an osteoinductive factor. Claim 20 requires the particles to have a diameter of 200 to 400 um. Claim 21 requires the binder to be present in an amount of 3 to 7 % w/w, based on the weight of the bone filler. Claim 22 requires the bone filler to have a solids content of 40-60% w/w.

Applicant's claim 17 is directed to a method for preparing the injectable bone filler according to claim 1, comprising mixing an organic binder with an affinity for calcium salt and a pharmaceutically acceptable buffer to prepare a gel, adding calcium salt particles to the gel, and homogenizing the organic binder/buffer mixture and the calcium salt particles to obtain the bone filler. Claim 18 requires cells, selected from the group consisting of stem cells, osteogenic cells, and osteoprogenitor cells to be seeded on the calcium salt particles before the salt particles are added to the gel, or for the cells to be introduced after combining the calcium salt particles and the gel.

Applicant's claim 19 is directed to a method for repairing an osseous defect comprising injecting the injectable bone filler of claim 1 into the defect.

Claims 1, 5, 6, 9, and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Frondoza et al (US 2001/0014475 A1).

Frondoza et al teach a cell-containing implant material for filling tissue voids. The implant material comprises cell-microcarrier aggregates, which consist of cells that are capable of secreting extracellular matrix grown on microcarrier particles (See Pg. 3, paragraph 0039). The aggregates may be provided in suspension and the suspension be implanted by injection to form the implant in situ (See Pg. 1, paragraph 0010). The injectable implant material may further comprise a binder material that aides in fixation and localization of the aggregate suspension after injection (See Pg. 2, paragraph 0010). Frondoza et al teach that a fluid medium, such as phosphate buffered saline, can be used to suspend the cell-containing aggregates and binder material to create the suspension for injection (See Pg. 7, paragraphs 0110-0115, especially 0112) (Claims 1 and 9).

The microcarrier particles of Frondoza et al consist of biocompatible, biodegradable material (See Pg. 1, paragraph 0008), including inorganic materials such as calcium phosphates, calcium carbonates, calcium sulfates or combinations thereof (which applicant calls calcium salt particles); organic materials such as collagen, gelatin, hyaluronic acid, chitosan, particles of tissue, such as bone or demineralized bone, cartilage, or other connective tissues (See Pg. 5, paragraph 0074). The microcarrier particles are in the size range of 100-500um, preferably 100-300um (See Pg. 5, paragraph 0073).

Frondoza et al exemplify chondrocytes as the type of extracellular matrix-secreting cell grown on the microcarrier particles, but also teach that other ECM-secreting cells, including osteoblasts and stem cells, which can differentiate into ECM-secreting cells, can also be seeded on the microcarriers to form the injectable aggregates (See Pg. 3, paragraph 0039) (Claim 1 and 13).

The binder material, used to aide in rapid adherence of the implant material to surrounding tissue, may include organic binders such as fibrin glues, collagens (which applicant calls a biogenic binder), combinations of fibrin and collagen, hyaluronic acid, alginate gels, chitosan, and hydrogels (See Pg. 3, paragraph 0038 & Pg. 5, paragraph 0082) (Claims 1, 5, and 6).

Therefore the reference anticipates the claimed subject matter.

Claims 1, 5, 6, 9, 12, 14 and 19 are rejected under 35 U.S.C. 102(e) as being anticipated by Schaefer et al (US Patent 6,703,038).

Schaefer et al teach an injectable bone substitute composition comprising cells, a soft matrix, and a setting matrix (See abstract). The cells of the composition are preferably osteoblasts or osteoblast precursors, or stem cells (See col. 3, ln 23-42). The cells are contained in the soft matrix, which consists of fibrin, formed by the reaction of fibrinogen and thrombin (See col. 2, ln 63-col. 3 ln 22); the soft matrix can further comprise additional agents including alginates, collagen gels, gelatin, and commercial fibrin glues (which applicant calls organic binders) (Claims 5 and 6). Growth factors such as bFGF, PDGF, VEGF, BMP, TGP-β may also be included in the soft matrix (See col. 3, ln 9-14) (which applicant calls angiogenic and osteoinductive factors) (Claims 12 and 14). The fibrin soft matrix is formed in the presence of phosphate buffered saline; therefore the composition further comprises phosphate buffered saline (See col. 5, ln 23-29) (Claims 1 and 9). The setting matrix comprises calcium phosphates, preferably hydroxyapatite cement (See col. 3, ln 56-60).

Schaefer et al teach the injectable bone substitute material can be used to fill osseous defects (See abstract) (Claim 19). Therefore the reference anticipates the claimed subject matter.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 3, 4, 8, 10, 11, and 17-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Frondoza et al (US 2001/0014475 A1), in view of Grimandi et al (J Biomed Mater Res, 1998), Lee et al (US Patent 6,953,594).

Frondoza et al teach a cell-containing implant material for filling tissue voids. The implant material comprises cell-microcarrier aggregates, which consist of cells that are capable of secreting extracellular matrix grown on microcarrier particles (See Pg. 3, paragraph 0039). The aggregates may be provided in suspension and may be implanted by injection to form the implant in situ (See Pg. 1, paragraph 0010). The injectable implant material may further comprise a binder material that aides in fixation and localization of the aggregate suspension after injection (See Pg. 2, paragraph 0010). Frondoza et al teach that a fluid medium, such as phosphate buffered saline, can be used to suspend the cell-containing aggregates and binder material to create the suspension for injection (See Pg. 7, paragraphs 0110-0115, especially 0112).

The microcarrier particles of Frondoza et al consist of biocompatible, biodegradable material, including inorganic materials such as calcium phosphates, calcium carbonates, calcium sulfates or combinations thereof (which applicant calls calcium salt particles) (See Pg. 5, paragraph 0074). The microcarrier particles are in the size range of 100-500um, preferably 100-300um (See Pg. 5, paragraph 0073) (Claims 4 and 20). Please note that where the claimed ranges overlap or lie inside ranges disclosed by the prior art a prima facie case of obviousness exists. See *In re Wertheim,* 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff,* 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990). Frondoza et al teach the microcarrier particles can include calcium phosphates, but they do not specifically teach which calcium phosphates can be used. However, at the time the invention was made it was well known that biphasic calcium phosphate (a 60/40 mixture of hydroxyapatite and β-calcium phosphate (both forms of calcium phosphate)) is a well suited bone substitute material due to its biocompatibility and ability to promote rapid bone ingrowth (See Grimandi et al, Pg. 661, col. 1), and thus one of ordinary skill in the art

would have been motivated to specifically use a biphasic calcium phosphate comprising a mixture hydroxyapatite and β-calcium phosphate as the microcarrier particles due to these beneficial properties (Claim 3). One would have expected success using biphasic calcium phosphate particles as the specific form of calcium phosphate for the microcarriers of Frondoza et al because Frondoza et al teach calcium phosphate can be used as the microcarrier particles substrate, and Grimandi et al teach biphasic calcium phosphate can successfully be used as cell carriers for injectable bone filler compositions, therefore one would expect successfully using that specific type of calcium phosphate as the calcium phosphate microcarrier in the composition of Frondoza et al.

Frondoza et al exemplify chondrocytes as the type of extracellular matrix-secreting cell grown on the microcarrier particles, but also teach that other ECM-secreting cells, including osteoblasts and stem cells, which can differentiate into ECM-secreting cells, can also be seeded on the microcarriers to form the injectable aggregates (See Pg. 3, paragraph 0039).

The binder material may include organic binders such as fibrin glues, collagens (which applicant calls a biogenic binder), combinations of fibrin and collagen, hyaluronic acid, alginate gels, chitosan, and hydrogels (See Pg. 3, paragraph 0038 & Pg. 5, paragraph 0082). Though Frondoza et al is silent on the amount of binder included in the injectable composition, it appears it is a result effective variable that directly effects the final solid content and binding capability of the injectable composition (Claims 8 and 21). Similarly, though Frondoza et al is silent on the viscosity and solids content of the injectable composition it appears these are result effective variables that would have been routinely optimized by one of ordinary skill in the art at the time the invention was made (Claims 10, 11 and 22).

Manipulating the solid content versus water content of a bone implant material is routine in the art, in support see Lee et al. Lee et al teach it is well within the purview of one of ordinary skill in the art to make empirical determinations of the appropriate amounts of solid reactants and water (buffer) to create an implant material of the desired consistency (viscosity) (See Lee et al, col. 17, ln 10-col. 18, ln

24). Lee et al teach different applications of bone filler compositions require different consistencies of the implant material. For example, direct injection into solid tissue, such as injection into cortical bone of an osteoporosis patient, a thinner consistency would be desired so the material runs into the various pores and defects to strengthen the overall bone; however, in the majority of cases the implant material needs to be as thick as possible, while still being pliable and injectable, in order to fill large, defined voids created by surgical removal of bone, or voids between broken bones (See Lee et al, col. 17, ln 53-col. 18, ln 24). One would expect success manipulating the solid content and the viscosity of the bone filler composition of Frondoza et al because means for such manipulations are known in the art, see Lee et al. Generally, differences in physical parameters such as concentration, viscosity or temperature, will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration, viscosity or temperature is critical or produces unexpected results; in the present application applicants have not demonstrated unexpected results using the claimed binder concentration (solid contents) or viscosity ranges. Where the general conditions of a claim are disclosed by the prior art it is not inventive to discover the optimum or workable ranges by routine experimentation, See *In re Aller,* 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Regarding the process of forming the injectable cell-containing implant material, Frondoza et al teach first seeding the cells onto the microcarrier particles (which can include calcium salt particles such as calcium phosphate, see above), suspending the cell-seeded microcarrier particles in a fluid medium, such as phosphate buffered saline, and then adding the binding material (in the form of fibrinogen and thrombin, which interact to form fibrin glue, the actual binding material) to the microcarrier-buffer mixture (See Pg. 7, paragraphs 0110-00114). Though Frondoza et al mix the ingredients in a different order than currently claimed, it would have been obvious to one of ordinary skill in the art at the time the invention was made to add the ingredients in any order, as selection of any order of mixing ingredients is prima facie obvious, particularly in the absence of any evidence showing unexpected benefits resulting

from the claimed sequence of mixing (Claims 17 and 18). See *In re Gibson*, 39 F.2d 975, 4 USPQ 230 (CCPA 1930).

Regarding the use of the cell-containing implant material, Frondoza et al teach the injectable cell-containing implant material can be used to fill tissue voids in situ; while Frondoza et al exemplify use of chondrocyte-containing implant material for the use of regeneration of cartilage (See, e.g. examples), they do suggest that the implant material can be used to regenerate and repair a variety of tissue types (See Pg. 3, paragraph 0039). Therefore, at the time the invention was made, it would have been well within the purview of one of ordinary skill in the art to seed the microcarrier particles with osteoblasts and other bone progenitor cells to create an implant material that can be injected into osseous defects in order to fill osseous voids (Claim 19). Frondoza et al teach that osteoblasts are among the acceptable cell types that can be seeded on the microcarrier particles (See Pg. 3, paragraph 0039), as they secrete extracellular matrix; therefore one of ordinary skill in the art would have been motivated to seed the microcarrier particles with osteoblasts and other bone progenitor cells to create an injectable implant material to correct osseous defects. One of ordinary skill in the art would have been motivated to use the osteoblast-containing injectable implant material of Frondoza et al to fill osseous defects in order to repair and regenerate voids left in bones after surgical removal or deterioration in order to correct the structural integrity of the bone. One would have expected success using the osteoblast-containing implant material of Frondoza et al as a bone filler composition for filling osseous defects because Frondoza et al teach the composition can be formulated with specific cell types to accommodate and regenerate desired tissues in situ.

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 12 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Frondoza et al (US 2001/0014475 A1), in view of Khouri et al (US Patent 6,110,482) and/or Bell et al (US Patent 6,110,482).

Frondoza et al teach a cell-containing implant material for filling tissue voids. The implant material comprises cell-microcarrier aggregates, which consist of cells that are capable of secreting extracellular matrix grown on microcarrier particles (See Pg. 3, paragraph 0039). The aggregates may be provided in suspension and the suspension be implanted by injection to form the implant in situ (See Pg. 1, paragraph 0010). The injectable implant material may further comprise a binder material that aides in fixation and localization of the aggregate suspension after injection (See Pg. 2, paragraph 0010). Frondoza et al teach that a fluid medium, such as phosphate buffered saline, can be used to suspend the cell-containing aggregates and binder material to create the suspension for injection (See Pg. 7, paragraphs 0110-0115, especially 0112).

The microcarrier particles of Frondoza et al consist of biocompatible, biodegradable material (See Pg. 1, paragraph 0008), including inorganic materials such as calcium phosphates, calcium carbonates, calcium sulfates or combinations thereof (which applicant calls calcium salt particles) (See Pg. 5, paragraph 0074).

Frondoza et al exemplify chondrocytes as the type of extracellular matrix-secreting cell grown on the microcarrier particles, but also teach that other ECM-secreting cells, including osteoblasts and stem cells, which can differentiate into ECM-secreting cells, can also be seeded on the microcarriers to form the injectable aggregates that would be suitable for bone tissue implants (See Pg. 3, paragraph 0039). Frondoza et al teach that bioactive peptides, such as growth factors, cytokines, integrins, adhesion molecules, etc, may be included in the composition (See Pg. 5, paragraph 0076), but they do not teach any specific bioactive agents. However, at the time the invention was made it would have been obvious to one of ordinary skill in the art to include known angiogenic and osteogenic (osteoinductive) growth

factors to aide in the growth, differentiation and survival of the implanted bone progenitor cells. At the time the invention was made it was well known to include growth factors such as BMPs, FGFs, PDGFs (which applicant calls osteoinductive factors) and TGF-β along with cell-containing bone implants, in support see Bell et al (See Bell et al, Pg. 8, paragraph 0069) (Claim 14). Additionally Khouri et al teach BMPs and TGF-βs also aid in vascularization and angiogenesis of bone tissue (See Khouri et al, col. 4, ln 18-65). Therefore, in order to recapitulate healthy bone formation in the defect area it would have been well within the purview of one of ordinary skill in the art to further include BMPs, FGFs, PDGFs (which applicant calls osteoinductive factors) and TGF-βs (which function as angiogenic factors) in the implant material of Frondoza et al (Claims 12 and 14). One of ordinary skill in the art would have been motivated to include these growth factors because Bell et al and Khouri et al teach these specific growth factors, when included in cell-containing bone implants, promote growth and differentiation of bone cells in the implant region and promote vasculogenesis of the implant area, thereby forming healthy, native bone tissue. One would expect success including these growth factors in the composition of Frondoza et al because Frondoza et al teach bioactive agents, including growth factors, can be included in their composition (See Frondoza et al, Pg. 5, paragraph 0076). Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 8, 10, 11, 17, 18, 21, and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schaefer et al (US Patent 6,703,038), in view of Lee et al (US Patent 6,953,594).

Schaefer et al teach an injectable bone substitute composition comprising cells, a soft matrix, and a setting matrix (See Schaefer et al, abstract). The cells of the composition are preferably osteoblasts or osteoblast precursors, or stem cells (See Schaefer et al, col. 3, ln 23-42).

The cells are contained in the soft matrix, which consists of fibrin, formed by the reaction of fibrinogen and thrombin (See Schaefer et al, col. 2, ln 63-col. 3 ln 22); the soft matrix can further

comprise additional agents including alginates, collagen gels, gelatin, and commercial fibrin glues (which applicant calls organic binders). The fibrin soft matrix is formed in the presence of phosphate buffered saline; therefore the composition further comprises phosphate buffered saline (See Schaefer et al, col. 5, ln 23-29). The setting matrix comprises calcium phosphates, preferably hydroxyapatite cement (See Schaefer et al, col. 3, ln 56-60).

While Schaefer et al teach fibrin, commercially available fibrin glue, collagens, gelatin and combinations thereof may be included in the 'soft matrix' (which applicant calls a binder) and calcium phosphates, particularly hydroxyapatite cements may be included in the 'setting matrix' (which applicant calls calcium salt particles), they are silent on the amount of these materials included in their injectable composition. However it appears the amounts and proportions of the components of the soft and setting matrices are result effective variables that directly effect the final solid content and mechanical properties of the injectable composition (Claims 8 and 21). Similarly, though Schaefer et al is silent on the viscosity and solids content of the injectable composition it appears these are result effective variables that would have been routinely optimized by one of ordinary skill in the art at the time the invention was made (See Schaefer et al, col. 4, ln 24-28) (Claims 10, 11 and 22).

Manipulating the solid content versus water content of a bone implant material is routine in the art, in support see Lee et al. Lee et al teach it is well within the purview of one of ordinary skill in the art to make empirical determinations of the appropriate amounts of solid reactants and water (buffer) to create an implant material of the desired consistency (viscosity) (See Lee et al, col. 17, ln 10-col. 18, ln 24). Lee et al teach different applications of bone filler compositions require different consistencies of the implant material. For example, direct injection into solid tissue, such as injection into cortical bone of an osteoporosis patient, a thinner consistency would be desired so the material runs into the various pores and defects to strengthen the overall bone; however, in the majority of cases the implant material needs to be as thick as possible, while still being pliable and injectable, in order to fill large, defined voids created

by surgical removal of bone, or voids between broken bones (See Lee et al, col. 17, ln 53-col. 18, ln 24). One would expect success manipulating the solid content and the viscosity of the bone filler composition of Schaefer et al because means for such manipulations are known in the art, see Lee et al. Generally, differences in physical parameters such as concentration, viscosity or temperature, will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration, viscosity or temperature is critical or produces unexpected results; in the present application applicants have not demonstrated unexpected results using the claimed binder concentration (solid contents) or viscosity ranges. Where the general conditions of a claim are disclosed by the prior art it is not inventive to discover the optimum or workable ranges by routine experimentation, See *In re Aller,* 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Regarding the process of forming the injectable bone substitute material, Schaefer et al teach first mixing the cells with a fibrinogen solution in phosphate buffered saline, then adding a calcium phosphate/thrombin mixture to the cell/fibrinogen mixture to form a cell/fibrin/calcium phosphate mixture to form the bone substitute material (See Schaefer et al, col. 10, ln 46- col. 11, ln 9). Though Schaefer et al mix the ingredients in a different order than currently claimed, it would have been obvious to one of ordinary skill in the art at the time the invention was made to add the ingredients in any order, as selection of any order of mixing ingredients is prima facie obvious, particularly in the absence of any evidence showing unexpected benefits resulting from the claimed sequence of mixing (Claims 17 and 18). See *In re Gibson*, 39 F.2d 975, 4 USPQ 230 (CCPA 1930).

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Allison M. Ford whose telephone number is 571-272-2936. The examiner can normally be reached on 7:30-5 M-Th, alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Allison M Ford
Examiner
Art Unit 1651